

Analysis of Anticoagulation Therapy Related Complications in Patients With Prosthetic Valves: Our Experience

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ABSTRACT

Purpose: The aim of this study is to analyze anticoagulation-related complications in patients following mechanical valve replacement and factors influencing the outcome.

Materials and Methods: A total of 250 patients were analyzed during OPD follow-up for anticoagulation-related complications and various factors influencing outcome. Patients received prosthetic valve at mitral and/or aortic or both.

Results: Out of 250 patients, 48% were male and 52% were female. The mean age was 41.9 ± 14.4 . A total of 139 had mitral valve replacement (MVR), 70 had aortic valve replacement (AVR), 40 had double valve replacement (DVR), and 1 patient had triple valve replacement. Valves implanted were mechanical bileaflet valve. The mean international normalization ratio (INR) in the study was 2.4 ± 0.56 . A total of 49 events occurred during follow-up, of which 4.5% per patient years were anticoagulation-related hemorrhagic events and 4.8% per patient years were thromboembolic events. Among thromboembolic events, valve thrombosis occurred in 10 patients and cerebrovascular accidents occurred in 11 patients. Mean INR for thromboembolic events was 1.46 ± 0.25 and anticoagulation-related hemorrhagic events was 4.4 ± 1.03 . Mortality rate was 1.6% in AVR, 4% in MVR, and 0.4% in DVR groups; about 34% of patients needed dose modification of Acenocoumarol and reason for derangement of INR was associated with infectious process and poor compliance; 85% of cases showed good compliance for daily anticoagulation therapy.

Conclusion: Anticoagulation for mechanical valve replacement can be managed with INR range of 2.0 to 2.5 in MVR and 1.5 to 2.0 in AVR with acceptable hemorrhagic and thromboembolic events. We must educate and counsel the patients during follow-up for better compliance to optimal anticoagulation.

Keywords: Anticoagulation, drug compliance, hemorrhage, INR, thromboembolism

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INTRODUCTION

The patients undergoing prosthetic valve replacement need careful follow-up in the postoperative period. To avoid early thromboembolic events, initiation of an efficacious early anticoagulation protocol is important. This is a big challenge to establish a balance between the risks of

under-anticoagulation (thromboembolic events) against those of over-anticoagulation (bleeding complications). We planned to conduct an analysis of approach to anticoagulation in such patients. The optimal approach to early postoperative anticoagulation after mechanical valve implantation remains controversial. Several design

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changes and modifications have been made to improve the longevity, hemodynamics, and thrombogenicity of newer generation mechanical valves.^[1] However, despite these advances, thromboembolism and anticoagulant-related bleeding continue to account for 75% of all complications after mechanical valve replacement.^[2] These complications occur more commonly within 6 months after implantation and can adversely affect mortality and morbidity. The need for life-long anticoagulation in patients with mechanical valves is universally accepted. The perioperative management of anticoagulation during non-cardiac surgery has been reviewed extensively.^[3] However, the approach to early postoperative anticoagulation after mechanical valve implantation is still a matter of debate. The optimal intensity and timing of anticoagulation to prevent early thromboembolism after valve replacement surgery without postoperative bleeding complications is unknown.

In general, a recent mechanical valve implantation is a strong risk factor for thromboembolic complications, especially in the first 3 to 6 months after surgery. In patients not receiving long-term anticoagulation therapy, the average rate of major thromboembolism is estimated to be 4 to 8 per 100 patient-years. This risk is reduced to 2.2 per 100 patient-years with antiplatelet therapy, and further reduced to 1 per 100 patient-years with oral anticoagulation. Thus, the utilization of postoperative anticoagulation therapy reduces the incidence of major embolism by approximately 75% and has become the standard of care for all patients with mechanical prosthesis.^[4-6] Echocardiography is the main diagnostic tool to assess valve malfunction in postoperative follow-up, for example, development of obstruction, infective endocarditis, and progressive disease in other valves, apart from assessment of cardiac chambers and their functions.

MATERIALS AND METHODS

The study was carried out at our department and institutional ethics committee approval was taken. The study was for a period of 15 months and included patients operated at our institute. All postoperative patients with prosthetic valve replacement coming for follow-up during the period of January 2012 to March 2013 were followed-up. After taking the consent, total 250 patients, who underwent mechanical valve replacement during this period, were enrolled in the study and the data were maintained during and thoroughly evaluated for any complications. All patients enrolled had a detailed clinical examination and investigations including ECG, chest X-ray, echocardiography, and CT scan wherever

required. All patients had valve replacement either with St. Jude Medical bileaflet mechanical valve (St. Jude Medical, Inc., St. Paul, Minn.) or ATS mechanical valve (ATS Medical, Inc, Minneapolis, Minn) depending upon the operating surgeon's choice. Postoperatively, patients were started on antiplatelet drugs (Aspirin 75 mg) and anticoagulants (Acenocoumarol) from the first post-op day itself. Acenocoumarol dosage was decided on the basis of INR levels and depending on the kind of valvular surgery, that is, for AVR, INR to be maintained between 2.0 and 2.5, whereas for MVR and DVR, INR targeted between 2.5 and 3.0. During follow-up visits, all patients were evaluated for any complications like bleeding episodes, thromboembolism, infection, or valve malfunctioning. During follow-up in OPD, detailed work-up including blood investigations and imaging tests were done to assess any complications. INR levels were tested weekly for the first postoperative month, then at interval of 2 weeks from second month onwards, and then once desired INR levels were achieved, the INR levels were checked at the interval of every 3 months. If required, patients were admitted until the optimum INR was achieved, and followed-up weekly until the proper control of INR was achieved.

The study analysis included evaluation of anticoagulation-related complications namely, thromboembolic and hemorrhagic events and morbidity and mortality related to these. Valve thrombosis, central nervous system complications, and bleeding events were defined according to Society of Thoracic Surgeons (STS) and American Association of Thoracic Surgeons (AATS) guidelines for reporting the morbidity and mortality of valve-related surgeries.^[7]

Statistical analysis

The data were analyzed using SPSS 14.0 (Statistical Package for Social Science, version 14.0). Categorical variables were expressed as percentages and continuous variables were expressed as mean \pm standard deviation. Events were defined as thromboembolic and hemorrhagic complications. Linearized event rates were calculated by dividing the total number of events by the patient-years of follow-up.

RESULTS

A total of 250 patients, coming for routine follow-up to OPD between January 2012 and March 2013, were enrolled for the study. The surgical procedures included are as follows: isolated MVR, isolated AVR, and multiple valve replacement. A total of 55% (n = 139) patients had

MVR, 28% (n = 70) patients had AVR, 16% (n = 40) had DVR (mitral and aortic), and 0.4% (n = 1) patient had tricuspid valve replacement along with mitral and aortic. Depending on single or multiple valves replaced, a total of 292 valves were replaced in the study group patients.

Incidence of complications, that is, mortality, thromboembolism, and anticoagulation-related hemorrhage among males was 3.2%, 3.6%, and 3.6% respectively, while among females, the incidence was 2.8%, 2.8%, and 2.8%, respectively.

Functional improvement

During postoperative OPD visit, all patients were clinically assessed on the basis of NYHA class, and it was found that out of 250 patients, 80% were in class I, 18% in class II, 0.8% in class III, and 0.4% in class IV.

Assessment of left ventricle function

The left ventricle (LV) function was normal (LVEF >50%) in 57% patient (n = 1430), moderately deranged in 32% (n = 81), and severely deranged in 26 (10.4%) had severe LV dysfunction (LVEF <35%).

In MVR group, 3.6% had thromboembolic events, 3.2% had bleeding events, and 4% expired during the study period. In AVR group, thromboembolism, bleeding events, pannus entrapment, and mortality were 2.4%, 0.8%, 0.4%, and 0.4%, respectively. Whereas, in DVR group, thromboembolism, bleeding events, and mortality were 1.2%, 3.2%, and 0.4%, respectively. TVR group had no mortality or morbidity event during the study period.

Among MVR patients, 8 patients had thromboembolic events (4 valvular thrombosis, 2 acute lower limb ischemia, and 3 had cerebral embolic events), 3 had anticoagulation-related hemorrhage, and over all 5 mortalities. Among DVR group, there was only one case of cardiac tamponade which had to be operated.

Assessment of anticoagulation

Mean INR range during follow-up was 2.86 ± 0.65 for MVR, 1.89 ± 0.578 for AVR, 2.97 ± 1.0 for DVR, and 2.4 for TVR. According to thromboembolic events and anticoagulation-related hemorrhagic events, mean INR in different surgical groups was analyzed. It was observed that mean INR in patients who had thromboembolic events was 1.48 in AVR group, 1.94 in MVR group, and 1.57 in DVR group. Mean INR in patients who had anticoagulation-related hemorrhagic events was 4.75 in AVR group, 4.03 in MVR group, and 4.68 in DVR group. Overall, mean INR in thromboembolic group was

Table 1: Table showing anticoagulation-related morbidity and mortality

Anticoagulant related hemorrhage:	17 (6.8%)
Peripheral (GIT, GU, Soft tissue, etc)	12 (4.8%)
ICH	5 (2%)
Thromboembolism:	18 (7.2%)
Peripheral (femoral artery)	2 (0.8%)
Cerebral	6 (2.4%)
Valvular	10 (4%)
Pannus entrapment	1 (0.4%)
Mortality	15 (6%)

1.46 ± 0.25 and in anticoagulation-related hemorrhage was 4.4 ± 1.03 [Table 1].

Drug compliance by patient

It was observed that the reason for deranged INR values was poor compliance to anticoagulant medication by patients; 15% of patients (n = 37) were observed to be noncompliant with daily intake of Acenocoumarol and 209 patients were showing good compliance for daily anticoagulation and frequent INR testing. In the group of poor compliance, 43% (n = 16) had thromboembolism, 8.1% (n = 3) expired, and 10.8% (n = 4) had anticoagulation-related hemorrhagic events. Whereas, in compliant patients, 5.7% (n = 12) had anticoagulation-related hemorrhagic events due to over anticoagulation, 3.3% (n = 7) expired, and there were no thromboembolic events in these patients.

Mortality

There were a total of 15 mortalities during study period. Six mortalities were due to cardiac cause (poor LV functions and low-cardiac output) and 5 due to non-cardiac cause (sepsis, cerebral infarct/hemorrhage, and respiratory complications). Cardiac causes of mortality included valve thrombosis and poor LV functions. One female patient died due to valve thrombosis as she got pregnant and she was noncompliant with the treatment. On telephonic follow-up, she was found to have been expired in a local hospital at her place. Two patients had anticoagulation-related cerebral bleed, 1 patient had CCF, 3 patients died because of respiratory complications, and 2 died of sepsis.

Readmission and surgical procedure

A total of 17 patients coming to out-patient department needed readmission due to anticoagulant-related hemorrhage (cerebral hemorrhage, peripheral hemorrhage, cardiac tamponade, and others). There were 7 patients of MVR, 2 of AVR, and 8 of DVR. Most of these patients were managed conservatively except one patient who presented with cardiac tamponade and had to be operated upon urgently. Gastrointestinal and genitourinary tracts were most common sites which were involved in peripheral sites of hemorrhage. Various events like

hematuria, hematemesis, haemoptysis, epistaxis, soft tissue hematoma, and ecchymosis were present in 12 patients. Two cerebral hemorrhagic events were fatal as there was severe intracranial hemorrhage. Deranged prothrombin time (PT/INR) and over anticoagulation was present in all the patients.

A total of 18 thromboembolic events occurred in patients during follow-up. There were 10 cases of valvular thrombosis, 2 cases of peripheral lower limb embolism, and 6 were of cerebral thromboembolic events including Transient ischemic attack (TIA) and major stroke.

There were 8 patients who had various systemic embolic events (2 peripheral and 6 cerebral), 5 patients of MVR, and 3 of AVR. Two patients of MVR had lower limb ischemia and underwent unilateral femoral embolectomy. Out of these, 1 patient had fatal outcome after embolectomy. Anticoagulation level was known in all events and was found to be insufficient in all patients. Ten patients presented with valve thrombosis during follow-up. Four events occurred after MVR, 3 events occurred after AVR, and 3 events after DVR. Insufficient coagulation was documented at the time of the event and several times before in few patients. In AVR group, thromboembolic rate was 1.705% per patient year, in MVR group 2.273% per patient year, and DVR group 0.882% per patient year. During follow-up, only 1 patient of AVR presented with pannus entrapment which necessitated reoperation and prosthesis replacement [Table 2].

There were 11 cerebrovascular accidents out of 250 patients. Six patients had ischemic infarcts, whereas 5 patients had severe intracranial hemorrhagic infarct. "Ischemic" accidents represented 4 TIA and 2 major infarcts. But none of them were fatal. Anticoagulation was insufficient in all

patients. "Hemorrhagic" infarct occurred in 5 patients and out of them, 2 mortalities occurred due to severe hemorrhagic infarct. Permanent impairment occurred in 2 cases. Diagnosis was made by CT scan as well as clinically. Over anticoagulation was documented in all patients who presented with intracranial hemorrhage. Independent risk factors for all cardio-vascular accident (CVA) were past history of systemic emboli, older age, cardiac failure, poor compliance with oral anticoagulants, or inadequate follow-up for INR levels.

DISCUSSION

Patients with prosthetic valve are at increased risk of complications due to deranged coagulation status as they need to take long-term oral anticoagulants postoperatively. This study analyzed the pattern of oral anticoagulant used and mortality and morbidity associated with anticoagulation during follow-up at a tertiary care hospital.

Our study included analysis of OPD follow-up of post valve surgery patients during a period of 15 months. Patients age ranged from 40 to 60 year (mean age 41.92 ± 14.42). Patients were operated for MVR 139 (55%), AVR 70 (28%), DVR 40 (16%), and 1 TVR (0.4%). As a standard protocol, all the patients were on Acenocoumarol during follow-up for anticoagulation.

Preoperatively, the majority group was of NYHA class III and IV (61% and 32%, respectively). Postoperatively, among 235 surviving patients at the time of follow-up study, 80% were in class I, 18% in class II, 0.8% in class III, and 0.4% in class IV. These results were similar to those reported by John *et al.*^[8]

Out of 250 patients, 18 patients had various thromboembolic events, that is, 4.8% per patient year (TIA (n = 6), peripheral

Table 2: Table showing distribution of symptoms

	MVR	AVR	DVR	TVR
Number of patients	139	70	40	1
Age	42.97	41.46	39.6	22
Male/Female	57/82	40/30	24/16	0/1
Pre-op NYHA I	0	2	0	0
Pre-op NYHA II	6	3	5	0
Pre-op NYHA III	78	45	28	1
Pre-op NYHA IV	55	20	7	0
INR	2.86±0.6	1.89±0.8	2.9±0.8	2.4
TE/ARH	1.94/4.03	1.48/4.75	1.57/4.68	
ARH	3.2%	0.8%	3.2%	Nil
	(2.273%/pt. yrs.)	(0.568%/pt. yrs.)	(1.705%/pt. yrs.)	
TE	3.6%	2.4%	1.2%	Nil
	(2.273%/pt. yrs.)	(1.705%/pt. yrs.)	(0.882%/pt. yrs.)	
Mortality	4%	1.6%	0.4	Nil
	(2.84%/pt. yrs.)	(1.136%/pt. yrs.)	(0.284%/pt. yrs.)	

INR levels and incidence mortality and morbidity in different type of valve surgeries. (MVR: mitral valve replacement; AVR: aortic valve replacement; DVR: double valve replacement; TVR: triple valve replacement; TE: thromboembolism; ARH: Anticoagulation related hemorrhage)

embolism ($n = 2$), and valve thrombosis ($n = 10$). In the AVR group, thromboembolism occurred in 6 patients. Of these, 1 event was defined as stroke and 2 events were defined as TIA. Three patients had valve thrombosis (1 was fatal). Thromboembolism occurred in 9 patients in the MVR group. Of these, 2 were defined as TIA and 1 as stroke. Two patients had peripheral embolic events and 4 patients had valve thrombosis.

Ikonomidis *et al.*^[9] in their study evaluated 25 years follow-up of 945 patients in whom St. Jude mechanical valve replacement was done. They found thromboembolism rate to be 3.2% per patient year and bleeding events of 3.8% per patient year (3% per patient-year in AVR group and 2.3% per patient-year in MVR group) and concluded that thromboembolism and bleeding remains the single biggest drawback to mechanical valve recipients. Their study did not include patients undergoing combined valve procedures. In their study, the operative mortality was 3% in AVR group and 5% in MVR group. These results are comparable to our results which had mortality of 1.6% and 4% in AVR and MVR group, respectively. Consistent with Ikonomidis *et al.*,^[9] we also found anticoagulation-related hemorrhage happened mostly in the MVR group. Akhtar *et al.*^[10] evaluated 507 patients with bileaflet, ball and cage valve, and single disc valve. They found 23 (1.13% per patient year) events due to thromboembolism and 41 (2.04% per patient year) bleeding events during follow-up of 10 years. They also observed that all patients had poor compliance to anticoagulation therapy despite repeated counseling. Results of our analysis matches that of Akhtar *et al.*^[10] Emery *et al.*^[11] studied 342 patients for 5 year follow-up (ATS Medical prosthetic valve). Their results showed mortality rate of 2.6%, bleeding events 4.9%, 7% neuro-embolic events, and 1 case of valve thrombosis. Our analysis results are in consistence with their results as well. Dhanya *et al.*^[12] analyzed 165 patients after valve surgery and use of anticoagulants. In their prospective observational study of 1 year duration, done on patients with mechanical valve replacement, they found thromboembolic complications occurred in 3.6% of cases and it occurred only when INR was <1.6 . Hemorrhagic complications occurred in 8.48% of patients. They used warfarin in 58.2% and Acenocoumarol in 41.8% patients. They also found that the most common complications are due to inadequate drug compliance by patients.

In our study, 10 cases of valve thrombosis occurred during the follow-up. There were 7 cases of partial thrombosis, successfully treated by thrombolytic therapy, 3 cases of complete obstructive fatal thrombosis. Three events occurred after AVR and 3 after MVR in which mitral valve was

thrombosed and 4 events occurred after MVR. Insufficient anticoagulation was documented at the time of the event. Buttard *et al.*^[13] reported that pannus formation may occur in 25% of patients as early as the first postoperative month. Pannus plays an important role in the mechanism of obstruction and could be the sole cause of mechanical valve thrombosis.^[14] In our study, there was only 1 patient in AVR group who presented with pannus formation and had to be operated for that and prosthesis replaced with another one.

The major complications following anticoagulation were bleeding and thrombosis and the adverse events occurred when the patients were outside therapeutic range of anticoagulation. Mean INR in our study group was 2.52 ± 1.02 . Mean INR range in patients with thromboembolic events was 1.46 ± 0.25 and in patients with anticoagulation-related hemorrhage was 4.4 ± 1.03 . However, it was noted that embolic complications occurred only at INR levels which were less than 1.6. John *et al.*^[8] observed an incidence of 0.5/100 patient-years for thromboembolic events and 0.31/100 patient-years for hemorrhagic events. According to the 8th American College of Chest Physicians guidelines,^[15] a low therapeutic INR range for Asian population has been advocated. These studies have shown low incidence of thromboembolic complications. Akhtar *et al.*^[10] state that Asian population are less prone to complications on a low INR 2 to 2.5 which is recommended by Japan as well as China. In the context of thrombotic complications occurring only in 3.6% of total patients at INR levels of <1.6 , we observe that in Indian population also, we need to broaden the target INR to 1.6 to 4 to prevent these complications.

There were 15% poor compliant patients who were not taking anticoagulant therapy regularly and 43% had thromboembolic events. Some patients belonged to distant locations and were living as migrant population in our area. They formed a major part of noncompliant group and did not follow-up regularly.

CONCLUSION

Anticoagulation for mechanical valve replacement can be managed with INR range of 2.0 to 2.5 in MVR and 1.5 to 2.0 in AVR with acceptable hemorrhagic and thromboembolic events. We observed that the most important factor to prevent these complications is repeated counseling and patient education to make them understand the importance of anticoagulation and recognition of the complications. The compliance to anticoagulation will reduce the incidence of morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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